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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/815,306	03/23/2001	Wen Y. Chen	035879/0120	4654

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EXAMINER	
YAEN, CHRISTOPHER H	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 01/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/815,306	CHEN ET AL.	
	Examiner	Art Unit	
	Christopher H. Yaen	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6,22,28,29,34-39,45-47,51-54 and 61-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,22,28,29,34-39,45-47,51-54 and 61-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/9/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Re: CHEN ET AL

1. The amendment filed 11/9/2005 is acknowledged and entered into the record. Accordingly, claims 2,7-21,23-27,30-33,40-44,48-50, and 55-60 are canceled without prejudice or disclaimer, and claims 61-71 are newly added.

2. Claims 1,3-6,22,28-29,34-39,45-47,51-54, and 61-71 are pending and examined on the merits.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections Maintained - 35 USC § 112, 1st paragraph

4. The rejection of claims 1,3-6,22,28,34-39,45-46, and 62-68 under 35 USC § 112, 1st paragraph is maintained for the reasons of record. Applicant argues that the specification and that art teaches hPRL and therefore any substitution at position 129 would be known to one of skill in the art. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record.

Given that the recited "hPRL" has not been associated with a specific structure (i.e. SEQ ID No: 1 or 34), and because the specification encompasses "conservative substitutions" of hRPL, one of skill in the art cannot possibly associate a specific function with structure. The specification defines hPRL as SEQ ID No: 1 (and now as newly added SEQ ID No: 34) or conservative substitutions thereof (see page 7, for example), however, the claims as currently recited do not associate any particular

structure with the claimed function. Applicant has described a single entity of hPRL (i.e. SEQ ID No: 1 or 34). The hPRL (i.e. hPRL with signal peptide - SEQ ID No: 1 or without signal peptide SEQ ID No: 34) sequence set forth by Applicant is not sufficient to describe a genus that includes polypeptides of variable structure. The courts in *Regents of the University of California v. Eli Lilly&Co* described that a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly&Co.*, 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The court have since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., __F.3d__,2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). In the instant specification, there are no other sequences set forth and there are no common structural features or common function specified by which one of skill could identify other members of the claimed genus. The functional limitation of claim 1, (receptor-antagonizing) is also not sufficient to identify the encompassed molecules. Thus the skilled artisan would not conclude that Applicant was in possession of the genus of hPRL polypeptides or conservative variants thereof. It is noted that what applicant is in possession of is a hPRL of SEQ ID No: 1 with a substitution at position 157 or a hPRL of SEQ ID No: 34 with an amino acid substitution at position 129.

Therefore the rejection of claims under 35 USC 112, 1st paragraph is maintained for the reasons of record.

New Arguments

Specification

5. The disclosure is objected to because of the following informalities:

a. The specification on pages 13 and 14, for example, recite sequences which have not been associated with any particular sequence identifiers. 37 CFR 1.82(d) requires the use of the assigned sequence identifier (SEQ ID No:) in all instances where the description of a patent application refers to a sequence and whenever a sequence or fragment thereof is claimed (see MPEP 2422.03).

b. The specification on page 16, for example, discloses hyperlinked text. 37 CFR 1.57(d) states that an incorporation by reference by hyperlink or other form of browser executable code is not permitted. Applicant must amend the specification to remove any recitation of hyperlinked materials recited. Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

6. Claims 1,3-6,22,28,34-39,45-46.51-54, and 62-71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the claims recite hPRL and hGH as the sole means of identifying the human prolactin and human growth hormone. With regard to hPRL, the specification defines hPRL as being either SEQ ID No: 1 or 34 and claims a substitution at position 129 of hPRL. It is unclear as to whether the substitution is found in SEQ ID No: 1 or 34. With regard to hGH, it is also well known in the art that hGH also comprises a signal

sequence (see exhibit 1, for example), does applicant intend for the substation to occur in a peptide with or without the signal sequence.

Appropriate correction and or clarification is required.

Claim Rejections - 35 USC § 112, 1st paragraph

7. Claims 1,3-6,22,28-29,34-39,45-47,51-54, and 61-71 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating prostate and breast cancers over expressing the human prolactin receptor (hPRL) comprising the administration of a receptor antagonizing domain of hPRL of SEQ ID No: 34 with a substitution at amino acid position 129 conjugated or fused to a cytokine selected from the group of IL-2, IL-12, and IFNγ, does not reasonably provide enablement for a method of treating any and all cancers comprising the administration of a protein comprising a receptor antagonizing domain of hPRL with a substitution at amino acid position 129 and any positive immunomodulatory cytokine as claimed. In addition, the claims are enabling for a method of treating cancers over-expressing human growth hormone receptor (hGHR) comprising the administration of hGH with an amino acid substitution at position 120 of the mature protein (i.e. without the signal peptide) wherein the substitution is anything other than alanine conjugated or fused to a cytokine selected from the group of IL-2, IL-12, and IFNγ, the claims are not enabling for a method of treating any and all cancers comprising the administering of a protein comprising a hGH with a substitution of alanine at position 120 and any positive immunomodulatory cytokine as claimed . The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a method of treating any cancer comprising the administration of a protein comprising an receptor antagonizing domain of either hPRL or hGH with an amino acid substitution at amino acid position 129 or 120, respectively, and an immunomodulatory domain, wherein the immunomodulatory domain is a cytokine. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims broadly encompass the treatment of any cancer comprising the administration of a protein that comprises a receptor antagonizing domain of either hPRL or hGH with a substitution at position 120 and 129, respectively, and a cytokine.

Quantity of experimentation

The amount of experimentation in this area is deemed high given that cancer is a highly unpredictable disease with different etiologies and treatment options. In addition, the art regarding the administration of cytokines for the purpose of eliciting an immune against a cancer is not all encompassing as claimed.

The unpredictability of the art and the state of the prior art

The treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive.

In addition, the art and the specification of the instant application teaches that hPRLR and hGHR are expressed in both normal and neoplastic cells, wherein cancers particularly breast and prostate cancers over-express the receptors by at least five times over the normal tissue (see page 2 of the specification, for example and Kelly *et al* (Mol. Cell. Endocrinology 2002;197:127-131) for a general review of hPRLR and hGHR). Thus one of skill in the art would not fully understand how to use the instant invention given that the administration of the claimed protein would target cells other

that the malignant or cancer cells, such as normal cells which express basal levels of the receptors.

Moreover, the art teaches that cytokines such as IL-2 are indeed effective for the treatment of cancers (see specification page 4, for example). However, the art also teaches that other cytokines can cause the proliferation of tumors due to the autocrine loop in lung cancers (see Rozengurt (Curr. Opin. Oncology 1999;11(2):116). In addition, the art also teaches that depending on the type of TH response (i.e TH1 or TH2), certain cytokines can either elicit or inhibit the proliferation of lymphomas (see Jones *et al* (Leuk Lymphoma. 2002 Jun;43(6):1313-21).

With regard to hGH, the specification clearly indicates that substitutions to the mature form of hGH (i.e. without the signal peptide) at position 120 can include any amino acid, except alanine (see page 17). Thus it is unclear how one of skill in the art could use a protein comprising a modification at postion 120 of hGH with an alanine.

All of this underscores the criticality of providing workable examples which is not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy.

Guidance in the specification

The specification provides a single working embodiment comprising a method of treating breast cancer with a hPRL-IL2 fusion protein, wherein there is a substation at position 129 of SEQ ID No: 34 with an arginine (i.e. G129R mutation) -- see example 10 for example.

However, the specification fails to provide working examples for the broad genus of cytokines that are able to "enhance the immune response against an abnormal cell, like a cancer cell (see page 9 of the specification) and methods of treating the broad class of cancers claimed. In addition, the specification fails to teach that a substitution of alanine at position 120 of hGH would be effective in antagonizing the GH receptor.

Level of skill in the art

The level of skill in the art is deemed to be high.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that ad, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the control and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States

only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 45 is rejected under 35 U.S.C. 102(e) as being anticipated by Fuh *et al* (US Patent 6,429,186). Fuh *et al* teach a method of treating breast cancer comprising the administration of a prolactin antagonist comprising a mutation at position 129 (see table IV, for example). In the absence of evidence to the contrary, the PRL protein itself can elicit an immune response as claimed, for the purposes of this claim, the "another domain" has been interpreted as being any other domain found in PRL. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H. Yaen whose telephone number is 571-272-0838. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on 571-272-0832. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Christopher Yaen
Art Unit 1643
January 10, 2006

CHRISTOPHER YAEN
PATENT EXAMINER